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A facile synthesis of 2-((5*R*)-2-oxo-5-oxazolidinyl)methyl)-1*H*-isoindole-1,3(2*H*)-dione†

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Synthesis of enantiomerically pure 2-((5*R*)-2-oxo-5-oxazolidinyl) methyl)-1*H*-isoindole-1,3(2*H*)-dione, a key precursor in the preparation of oxazolidinone class of antibacterial agents starting from (*S*)-epichlorohydrin has been achieved.

Keywords: Oxazolidinone, antibacterial, epichlorohydrin, enantiomerically pure, phthalimide

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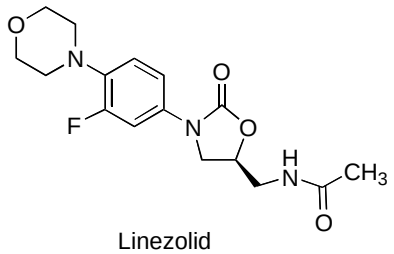
Oxazolidinones have emerged as a very important class of compounds in drug development, especially in the area of antibacterials[1] and inhibitors of monoamine oxidase[2]. They also have potent pharmacological effects as cytokine modulators[3], sigma receptors[4], phychotropics[5], antiallergy agents[6], antibiotics[7], intermediates in the synthesis of rennin inhibitors[8], β-lactam and macrolide antibiotics[9], immunosupressants[10] and in various other applications[11].



Linezolid

Oxazolidinones are the first new class of synthetic antibacterial agents introduced ever since the discovery of quinolones more than 30 years ago. The oxazolidinone antibacterial agents show activity against gram-positive bacteria. Pharmacia group discovered Linezolid[1b,c], which was found to be the first candidate among oxazolidinones which were effective against serious attacks by gram-positive human pathogens, *e.g.* methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) without side effects like severe toxicity. Linezolid is the first drug of this class approved by FDA under the trade name Zyvox in April 2000. In this class, over 250 molecules having antibacterial activity are in different stages of clinical trials. Most of the molecules, including Linezolid, comprise 5-aminomethyl 3-aryl oxazolidinone moiety as the basic skeleton.

A common strategy for preparation of 5-amino-methyl-3-aryl oxazolidinone in the Linezolid is deprotonation of the aryl carbamate with BuLi and reaction with (*R*)-glycidylbutyrate to give the corresponding 5(*S*)-hydroxymethyloxazolidinone[1c]. The lithium anion of the carbamate was necessary to obtain a useful yield of the desired oxazolidinones. In an alternative strategy, the aryl oxazolidinones could be obtained from aryl isocyanates and (*R*)-glycidyl-butyrate[1a]. The preparation of aryl isocyanate is cumbersome from all substituted aryl amines. From the literature, it is evident that the 2-((5*R*)-2-oxo-5-oxazolidinyl)methyl)-1*H*-isoindole-1,3(2*H*)-dione could be useful for the preparation of 5-aminomethyl-3-aryl oxazolidinone moiety[12]. It provides access to various arylsubstituted oxazolidinone analogs by coupling with corresponding arylhalides, which is already well documented[13]. The 2-((5R)-2-oxo-5-oxazolidinyl)-methyl)-1H-isoindole-1,3(2H)-dione was prepared previously from (R)-hydroxymethyl-2-oxazolidin-ones[12], which was prepared in a multi step synthesis

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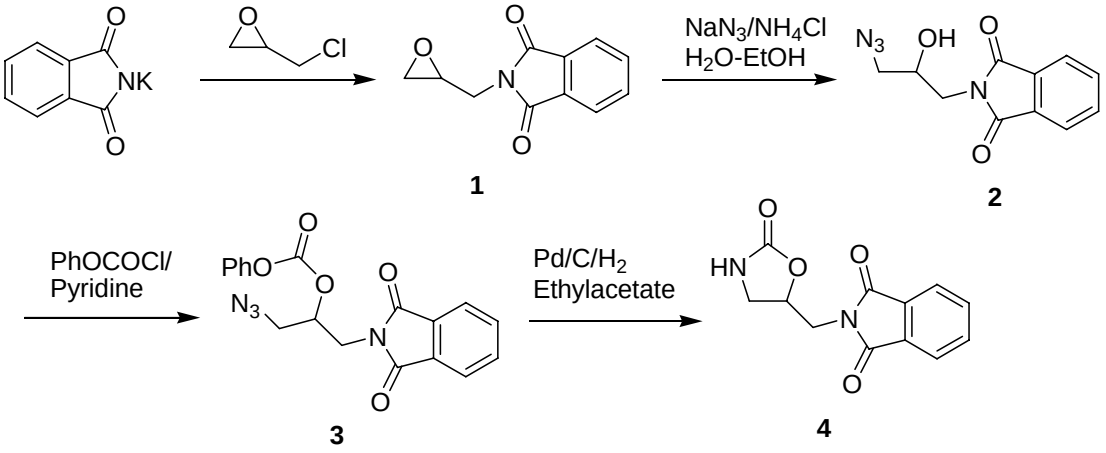
from D-malic acid[14]. In this paper is reported a convenient procedure for the preparation of enantiomerically pure 2-((5R)-2-oxo-5-oxazolidinyl)methyl)-1H-isoindole-1,3(2H)-dione from (R)-epichlorohydrin without racemization *via* (R)-chloromethyl-2-oxazolidinone.

Results and Discussion

N-(2,3-epoxypropyl)phthalimide 1 was prepared by condensing epichlorohydrin with potassium phthalimide[15]. Following the classical method[16], the compound 1 was reacted with NaN_3 in H_2O/EtOH mixture in mild acidic conditions using NH_4Cl to obtain corresponding azido alcohol **2**. The alcohol **2** was reacted with phenylchloroformate in DCM with pyridine as base to give phenyl carbonate derivative **3**. Further, it was converted to 2-(2-oxo-5-oxazolidinyl)-methyl)-1*H*-isoindole-1,3(2*H*)-dione **4** by reductive cyclization using Pd/C. Earlier, the reductive cyclization[17] was studied using various carbonate derivatives and among them phenyl carbonate gives the desired cyclization (**Scheme I**).

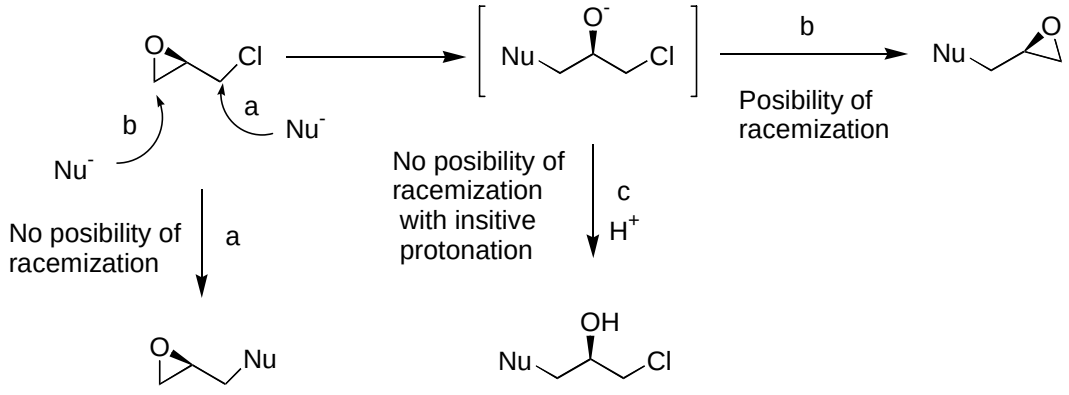
Later, it was decided to carry out stereoselective synthesis of 2-((5R)-2-oxo-5-oxazolidinyl)methyl)-1H-isoindole-1,3(2H)-dione from chiral N-(2,3-epoxypropyl)- phthalimide. Accordingly, the (R)-epichlorohydrin was reacted with phthalimide in the presence of K_2CO_3in CH_3CN. It was possible to isolate only the racemised N-(2,3-epoxypropyl)-phthalimide. The racemization was minimized to a large extent by reacting potassium phthalimide and (R)-epichlorohydrin in the absence of solvent and base K_2CO_3. Under these conditions racemisation to the extent of 7-15% was observed. It is obvious that racemization can not be avoided totally while condensing a nucleophile (like phthalimide and azide) with the epichlorohydrin under dry conditions. The nucleophilic attack on epichlorohydrin leading to racemization is shown in the mechanism (**Scheme II**). The (R)-N-(2,3-epoxypropyl)phthalimide was prepared earlier from (R)-glycidol[18].

Finally, a stereoselective synthesis of 2-((5*R*)-2-oxo-5-oxazolidinyl)methyl)-1*H*-isoindole-1,3(2*H*)-dione from (*R*)-epichlorohydrin was accomplished

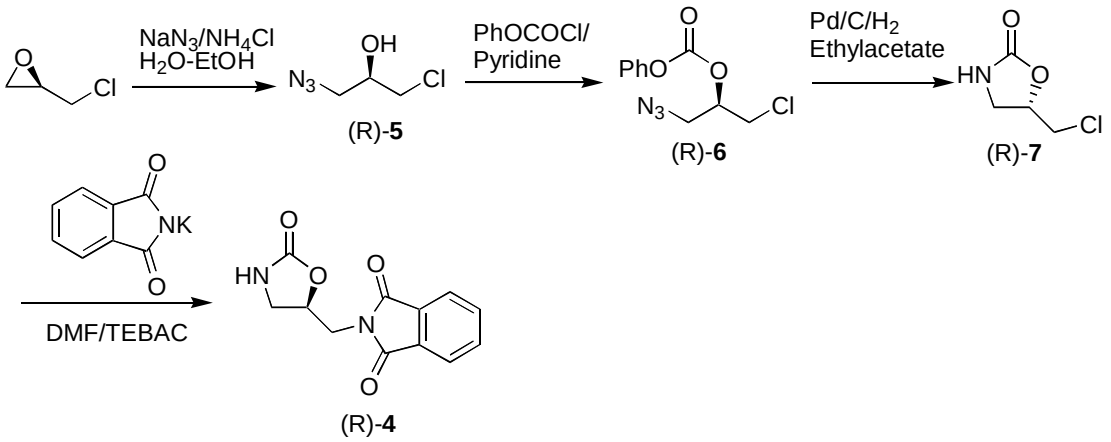


1 **2** **3** **4**

Scheme I



Scheme II



Scheme III

through (*R*)-chloromethyl-2-oxazolidinone (*R*)-**7**. The (*R*)-epichlorohydrin was reacted with NaN_3 in H_2O/EtOH mixture using NH_4Cl to obtain (2*R*)-1-azido-3-chloropropane-2-ol ((*R*)-**5**) without racemization. Compound (*R*)-**5** was reacted with phenylchloroformate in pyridine to obtain the phenyl carbonate derivative (*R*)-**6**. (*R*)-**6** was further converted to (*R*)-chloromethyl-2-oxazolidinones ((*R*)-**7**) by reductive cyclization using Pd/C. Compound (*R*)-**7** was reacted with potassium phthalimide in DMF under PTC conditions to obtain the desired 2-((5*R*)-2-oxo-5-oxazolidinyl)methyl)-1*H*-isoindole-1,3(2*H*)-dione ((*R*)-**4**). This sequence of reactions has been illustrated in **Scheme III**.

To conclude, a stereoselective method was developed for the preparation of 2-((5*R*)-2-oxo-5-oxazolidinyl)methyl)-1*H*-isoindole-1,3(2*H*)-dione, a very important moiety in the oxazolidinone class of antibacterial agents.

Experimental Section

Melting points were determined on Buchi 535 melting point apparatus and are uncorrected. IR spectra were recorded in KBr/$CHCl_3$ on a Perkin-Elmer 1650 Spectrometer. ^1H and ^{13}C NMR were recorded in $CDCl_3$ using Varian Gemini 200 MHz spectrometer (chemical shifts in δ ppm) with TMS as internal standard and mass spectra were recorded on a HP-5989A spectrometer. The Analytical Research Department of Dr. Reddy's Research Foundation carried out all analytical work. All the organic extracts were dried over sodium sulfate after work-up.

The dry reactions were carried out under nitrogen atmosphere with magnetic/mechanical stirring. Unless otherwise mentioned, all the solvents and reagents used were of LR grade. TLC was performed on precoated silica-gel plates, which were visualized using UV light and sulphuric acid/ethanol (5:95) charring. Flash column-chromatography was carried out on silica gel (230-400 mesh) unless otherwise stated.

General procedure for the preparation of azido alcohols. To a cooled solution of sodium azide (16.86 g, 0.259 moles) and ammonium chloride (13.87 g, 0.259 moles) in water (80 mL), a solution of oxirane ((*R*)-epichlorohydrin, **1** (0.216 moles) in ethanol (20 mL) was added. The reaction mixture was stirred at 0°C for 1 h and then allowed to come to RT and maintained overnight. The reaction mixture was diluted with water (80 mL) and extracted with ethyl acetate (3 ×100 mL). The combined extract was washed with water (3 ×75 mL) and concentrated to get the respective azido alcohol (**2** or (*S*)-**5**). Crude **2** was stirred in pet. ether to afford pure **2** as a white solid (m.p. 64-6°C). The (*S*)-**5** was obtained after flash column chromatography as a liquid ($[\alpha]^{25}_D$=+1.7 (C: 1.0, $CHCl_3$)). The spectral characterization data for **2** and (*R*)-**5** are given in **Table I**.

General procedure for the preparation of phenyl carbonate derivative. To a solution of azido alcohol (**2** or **5**, 0.0369 moles), pyridine (5 mL) and DCM (50 mL), phenylchloroformate (6.35 g, 0.04059 moles) was added dropwise at 0°C. After stirring at 0°C for 1 h, the reaction mixture was poured into water and the DCM layer was separated. The aqueous layer was extracted with DCM (100 mL) and the combined organic extract was washed with dil.HCl (20 mL) followed by water (2 ×20 mL) and then concentrated to get the corresponding phenyl carbonate derivative (**3** or (*R*)-**6**). The compound **3** was taken for further reductive cyclization without purification. The (*R*)-**6** was obtained after flash

Table I — Spectral characterization data of various compounds prepared

Compd	Yield (%)	^{1}H NMR δ, ppm	^{13}CNMR δ, ppm	MS m/z (M+1)
2	74.2	3.1 (s, 1H, -OH, D_2O exchangeable), 3.5 (m, 2H, -CH_2N_3), 3.9 (m, 2H, -CH_2N-), 4.2 (m, 1H, -CHOH), 7.8-8.0 (m, 4H, Ar-H).	41.52, 54.43, 69.13, 123.39, 131.64, 134.16, 168.61.	247
4	92	3.5 (m, 1H, -C*H*-*H*-NH-), 3.75 (t, 1H, -C*H*-*H*-NH-), 3.9 (dd, 1H, -CH-*H*-N-, *J*=5.6, 14.23), 4.1 (dd, 1H, -CH-*H*-N-, *J*=7.0, 14.23), 4.95 (m, 1H, -CHO-), 5.7 (s, 1H, -NH, D_2O exchangeable), 7.7-7.95 (m, 4H, Ar-H.).	40.42, 43.32, 72.48, 123.10, 131.34, 133.94, 158.49, 167.54.	247
(*R*)-**4**	84			
(*R*)-**5**	65	2.4 (s, 1H, -OH, D_2O exchangeable), 3.28-3.45 (m, 4H, -CH_2N_3 and -CH_2Cl), 4.0 (m, 1H, -C*H*OH).	46.02, 53.28, 70.11	136
(*R*)-**6**	91	3.65-3.8 (m, 4H, -CH_2N_3 and -CH_2Cl), 5.05 (m, 1H, -CHO-), 7.15-7.45 (m, 5H, -Ar-H).	41.87, 50.53, 75.63, 120.69, 126.21, 129.42, 150.69, 152.59.	256
(*R*)-**7**	90	3.45-3.8 (m, 4H, -CH_2NH- and -CH_2Cl), 4.8 (m, 1H, -CHO-), 6.3 (s, 1H, -NH, D_2O exchangeable).	43.37, 44.57, 74.61, 159.38.	136, 138 (M+3

column chromatography as a syrup ($[\alpha]^{25}_D$ = -19.5 (C: 1.0, $CHCl_3$)). The spectral characterization data for (*R*)-**6** are given in **Table I**.

General procedure for the reductive cyclization. A solution of phenylcarbonate derivative (**3** or (*R*)-**6)** (0.0234 mole) in ethyl acetate (60 mL) was hydrogenated in a Parr apparatus in the presence of 5% Pd/C (10 % w/w) at 10-15 psi H_2 pressure for about 6 h. The catalyst was filtered out on a pad of celite and the filtrate was concentrated to get the corresponding cyclized compound (**4** or (*R*)-**7**). The compound **4** was subjected to purification in IPA to afford racemic **4** as a white solid (m.p. 206-08°C). The (*R*)-**7** was purified by flash column chromatography to obtain pure (*R*)-**7** as white solid (m.p. 75-7°C; $[\alpha]^{25}_D$=-16.1 (C: 0.7, CH_2Cl_2)). The spectral characterization data for **4** and (*R*)-**7** are given in **Table I**.

Preparation of 2-((5*R*)-2-oxo-5-oxazolidinyl)-methyl)-1*H*-isoindole-1,3(2*H*)-dione. To a solution of (*R*)-**7** (0.5 g, 0.0037 moles) in DMF (5 mL), potassium phthalimide (0.683 g, 0.0037 moles) and catalytic amount of triethylbenzylammonium chloride were added and the mixture stirred at 80°C for 12 h. The reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (3×30 mL). The combined organic extract was washed with water (2×20 mL) and evaporated. The obtained solid was stirred in IPA (15 mL) to get (*R*)-**4** as a solid (m.p.195-97°C; $[\alpha]^{25}_D$=67.1 (C: 1.0, $CHCl_3$). The spectral characterization data for (*R*)-**4** are given in **Table I**.

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